



The NEW ENGLAND JOURNAL of MEDICINE

[HOME](#) | [SEARCH](#) | [CURRENT ISSUE](#) | [PAST ISSUES](#) | [COLLECTIONS](#) | [HELP](#)

Please [sign in](#) for full text and personal services

ORIGINAL ARTICLE

Volume 324:429-436

February 14, 1991

Number 7

[Next](#) ►

Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group

EJ Ziegler, CJ Fisher, CL Sprung, RC Straube, JC Sadoff, GE Foulke, CH Wortel, MP Fink, RP Dellinger, NN Teng, and et al.

Abstract

BACKGROUND. HA-1A is a human monoclonal IgM antibody that binds specifically to the lipid A domain of endotoxin and prevents death in laboratory animals with gram-negative bacteremia and endotoxemia. **METHODS.** To evaluate the efficacy and safety of HA-1A, we conducted a randomized, double-blind trial in patients with sepsis and a presumed diagnosis of gram-negative infection. The patients received either a single 100-mg intravenous dose of HA-1A (in 3.5 g of albumin) or placebo (3.5 g of albumin). Other interventions, including the administration of antibiotics and fluids, were not affected by the study protocol. **RESULTS.** Of 543 patients with sepsis who were treated, 200 (37 percent) had gram-negative bacteremia as proved by blood culture. For the patients with gram-negative bacteremia followed to death or day 28, there were 45 deaths among the 92 recipients of placebo (49 percent) and 32 deaths among the 105 recipients of HA-1A (30 percent; $P = 0.014$). For the patients with gram-negative bacteremia and shock at entry, there were 27 deaths among the 47 recipients of placebo (57 percent) and 18 deaths among the 54 recipients of HA-1A (33 percent; $P = 0.017$). Analyses that stratified according to the severity of illness at entry showed improved survival with HA-1A treatment in both severely ill and less severely ill patients. Of the 196 patients with gram-negative bacteremia who were followed to hospital discharge or death, 45 of the 93 given placebo (48 percent) were discharged alive, as compared with 65 of the 103 treated with HA-1A (63 percent; $P = 0.038$). No benefit of treatment with HA-1A was demonstrated in the 343 patients with sepsis who did not prove to have gram-negative bacteremia. For all 543 patients with sepsis who were treated, the mortality rate was 43 percent among the recipients of placebo and 39 percent among those given HA-1A ($P = 0.24$). All patients tolerated HA-1A well, and no anti-HA-1A antibodies were detected. **CONCLUSIONS.** HA-1A is safe and effective for the treatment of patients with sepsis and gram-negative bacteremia.

THIS ARTICLE

► [Return to Search Result](#)

TOOLS & SERVICES

- [Add to Personal Archive](#)
- [Add to Citation Manager](#)
- [Notify a Friend](#)
- [E-mail When Cited](#)

MORE INFORMATION

- [Find Similar Articles](#)
- [PubMed Citation](#)

Source Information

Department of Medicine, University of California, San Diego.

This article has been cited by other articles:

- Delgado, M., Pozo, D., Ganea, D. (2004). The Significance of Vasoactive Intestinal Peptide in Immunomodulation. *Pharmacological Reviews* 56: 249-290 [Abstract] [Full Text]
- Merx, M. W., Liehn, E. A., Janssens, U., Lutticken, R., Schrader, J., Hanrath, P., Weber, C. (2004). HMG-CoA Reductase Inhibitor Simvastatin Profoundly Improves Survival in a Murine Model of Sepsis. *Circulation* 109: 2560-2565 [Abstract] [Full Text]
- Krogh-Madsen, R., Moller, K., Dela, F., Kronborg, G., Jauffred, S., Pedersen, B. K. (2004). Effect of hyperglycemia and hyperinsulinemia on the response of IL-6, TNF- α , and FFAs to low-dose endotoxemia in humans. *Am. J. Physiol.* 286: E766-E772 [Abstract] [Full Text]
- Matsuda, N., Hattori, Y., Zhang, X.-H., Fukui, H., Kemmotsu, O., Gando, S. (2003). Contractions to Histamine in Pulmonary and Mesenteric Arteries from Endotoxemic Rabbits: Modulation by Vascular Expressions of Inducible Nitric-Oxide Synthase and Histamine H1-Receptors. *J. Pharmacol. Exp. Ther.* 307: 175-181 [Abstract] [Full Text]
- Tobin, M. J. (2003). The Role of a Journal in a Scientific Controversy. *Am J Respir Crit Care Med* 168: 511-511 [Full Text]
- van der Flier, M., Geelen, S. P. M., Kimpen, J. L. L., Hoepelman, I. M., Tuomanen, E. I. (2003). Reprogramming the Host Response in Bacterial Meningitis: How Best To Improve Outcome?. *Clin. Microbiol. Rev.* 16: 415-429 [Abstract] [Full Text]
- Kaptchuk, T. J (2003). Effect of interpretive bias on research evidence. *BMJ* 326: 1453-1455 [Full Text]
- Vandenbroucke, J. P., de Craen, A. J.M. (2001). Alternative Medicine: A "Mirror Image" for Scientific Reasoning in Conventional Medicine. *Ann Intern Med* 135: 507-513 [Abstract] [Full Text]
- Bone, R. C. (1996). Immunologic Dissonance: A Continuing Evolution in Our Understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS). *Ann Intern Med* 125: 680-687 [Abstract] [Full Text]
- Cross, A. S. (1994). Antiendotoxin Antibodies: A Dead End?. *Ann Intern Med* 121: 58-60 [Full Text]
- McCloskey, R. V., Straube, R. C., Sanders, C., Smith, S. M., Smith, C. R. (1994). Treatment of Septic Shock with Human Monoclonal Antibody HA-1A: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Intern Med* 121: 1-5 [Abstract] [Full Text]
- Casey, L. C., Balk, R. A., Bone, R. C. (1993). Plasma Cytokine and Endotoxin Levels Correlate with Survival in Patients with the Sepsis Syndrome. *Ann Intern Med* 119: 771-778 [Abstract] [Full Text]
- Nasraway, S. A. (2003). The Problems and Challenges of Immunotherapy in Sepsis. *Chest* 123: 451S-459 [Abstract] [Full Text]
- Chaudry, I. H. (1999). Sepsis: Lessons Learned in the Last Century and Future Directions. *Arch Surg* 134: 922-929 [Full Text]
- Calvano, S. E., Coyle, S. M., Barbosa, K. S., Barie, P. S., Lowry, S. F. (1998). Multivariate Analysis of 9 Disease-Associated Variables for Outcome Prediction in Patients With Sepsis. *Arch Surg* 133: 1347-1350 [Abstract] [Full Text]
- Angus, D. C., Birmingham, M. C., Balk, R. A., Scannon, P. J., Collins, D., Kruse, J. A., Graham, D. R., Dedhia, H. V., Homann, S., MacIntyre, N., for the E5 Study Investigators, (2000). E5 Murine Monoclonal Antiendotoxin Antibody in Gram-Negative Sepsis: A Randomized Controlled Trial. *JAMA* 283: 1723-1730 [Abstract] [Full Text]
- Ye, J., Wang, L., Zhang, X., Tantishaiyakul, V., Rojanasakul, Y. (2003). Inhibition of TNF- α gene expression and bioactivity by site-specific transcription factor-binding oligonucleotides. *Am. J. Physiol.* 284: L386-394 [Abstract] [Full Text]

- Hotchkiss, R. S., Karl, I. E. (2003). The Pathophysiology and Treatment of Sepsis. *N Engl J Med* 348: 138-150 [\[Full Text\]](#)
- Cranshaw, J, Griffiths, M J D, Evans, T W (2002). The pulmonary physician in critical care c 9: Non-ventilatory strategies in ARDS. *Thorax* 57: 823-829 [\[Abstract\]](#) [\[Full Text\]](#)
- RAPONI, G., GHEZZI, M. C., LUN, M. T., BIGOTTI, G., NATALI, P. G., MANCINI, C. (2000). Protective features of monoclonal antibodies to Escherichia coli during experimental infection of mice with homologous and heterologous serotypes of E. coli. *J Med Microbiol* 49: 253-260 [\[Abstract\]](#) [\[Full Text\]](#)
- Giacometti, A., Cirioni, O., Ghiselli, R., Mocchegiani, F., Del Prete, M. S., Viticchi, C., Kamysz, W., Lempicka, E., Saba, V., Scalise, G. (2002). Potential Therapeutic Role of Cationic Peptides in Three Experimental Models of Septic Shock. *Antimicrob. Agents Chemother.* 46: 2132-2136 [\[Abstract\]](#) [\[Full Text\]](#)
- Hebert, P. C., Cook, D. J., Wells, G., Marshall, J. (2002). The Design of Randomized Clinical Trials in Critically Ill Patients*. *Chest* 121: 1290-1300 [\[Abstract\]](#) [\[Full Text\]](#)
- Drewe, E, Powell, R J (2002). Clinically useful monoclonal antibodies in treatment. *J Clin Pathol* 55: 81-85 [\[Abstract\]](#) [\[Full Text\]](#)
- (1991). MONOCLONAL ANTIBODY IS EFFECTIVE IN GRAM-NEGATIVE SEPSIS. *Journal Watch (General)* 1991: 1-1 [\[Full Text\]](#)
- Cirioni, O., Giacometti, A., Ghiselli, R., Mocchegiani, F., Fineo, A., Orlando, F., Del Prete, M. S., Rocchi, M., Saba, V., Scalise, G. (2002). Single-Dose Intraperitoneal Magainins Improve Survival in a Gram-Negative-Pathogen Septic Shock Rat Model. *Antimicrob. Agents Chemother.* 46: 101-104 [\[Abstract\]](#) [\[Full Text\]](#)
- Sheridan, R. L. (2001). A Great Constitutional Disturbance. *N Engl J Med* 345: 1271-1272 [\[Full Text\]](#)
- Hinds, C J (2001). Treatment of sepsis with activated protein C. *BMJ* 323: 881-882 [\[Full Text\]](#)
- Kolb-Maurer, A., Unkmeir, A., Kammerer, U., Hubner, C., Leimbach, T., Stade, A., Kampgen, E., Frosch, M., Dietrich, G. (2001). Interaction of Neisseria meningitidis with Human Dendritic Cells. *Infect. Immun.* 69: 6912-6922 [\[Abstract\]](#) [\[Full Text\]](#)
- Emmanuilidis, K., Weighardt, H., Maier, S., Gerauer, K., Fleischmann, T., Zheng, X. X., Hancock, W. W., Holzmann, B., Heidecke, C.-D. (2001). Critical Role of Kupffer Cell-Derived IL-10 for Host Defense in Septic Peritonitis. *J Immunol* 167: 3919-3927 [\[Abstract\]](#) [\[Full Text\]](#)
- Thomas, C. J., Surolia, N., Surolia, A. (2001). Kinetic and Thermodynamic Analysis of the Interactions of 23-Residue Peptides with Endotoxin. *J. Biol. Chem.* 276: 35701-35706 [\[Abstract\]](#) [\[Full Text\]](#)
- Sanlioglu, S., Williams, C. M., Samavati, L., Butler, N. S., Wang, G., McCray, P. B. Jr., Ritchie, T. C., Hunninghake, G. W., Zandi, E., Engelhardt, J. F. (2001). Lipopolysaccharide Induces Rac1-dependent Reactive Oxygen Species Formation and Coordinates Tumor Necrosis Factor-alpha Secretion through IKK Regulation of NF-kappa B. *J. Biol. Chem.* 276: 30188-30198 [\[Abstract\]](#) [\[Full Text\]](#)
- Sprong, T., Stikkelbroeck, N., van der Ley, P., Steeghs, L., van Alphen, L., Klein, N., Netea, M. G., van der Meer, J. W. M., van Deuren, M. (2001). Contributions of Neisseria meningitidis LPS and non-LPS to proinflammatory cytokine response. *J Leukoc Biol* 70: 283-288 [\[Abstract\]](#) [\[Full Text\]](#)
- Greisman, S. E., Johnston, C. A., Gosnell, M. S., Kapur, S., Kupfer, Y., Tessler, S., Ott, A., Verbrugh, H. A., O'Connor, P. E., Bernard, G. R., Ely, E. W., Helterbrand, J. D. (2001). Recombinant Human Activated Protein C for Severe Sepsis. *N Engl J Med* 345: 219-221 [\[Full Text\]](#)
- Fisher, C. J., Agosti, J. M., Opal, S. M., Lowry, S. F., Balk, R. A., Sadoff, J. C., Abraham, E., Schein, R. M.H., Benjamin, E., The Soluble TNF Receptor Sepsis Study Group, (1996). Treatment of Septic Shock with the Tumor Necrosis Factor Receptor:Fc Fusion Protein. *N Engl J Med* 334: 1697-1702 [\[Abstract\]](#) [\[Full Text\]](#)
- Pizzo, P. A. (1993). Management of Fever in Patients with Cancer and Treatment-Induced Neutropenia. *N Engl J Med* 328: 1323-1332 [\[Full Text\]](#)
- Weinberger, S. E. (1993). Recent Advances in Pulmonary Medicine- Second of Two Parts. *N Engl J Med* 328: 1462-1470 [\[Full Text\]](#)
- Parrillo, J. E. (1993). Pathogenetic Mechanisms of Septic Shock. *N Engl J Med* 328: 1471-1478 [\[Full Text\]](#)
- Stubblefield, P. G., Grimes, D. A. (1994). Septic Abortion. *N Engl J Med* 331: 310-314 [\[Full Text\]](#)
- Kollef, M. H., Schuster, D. P. (1995). The Acute Respiratory Distress Syndrome. *N Engl J Med* 332:

27-37 [Full Text]

- Warren, H. S. (1997). Strategies for the Treatment of Sepsis. *N Engl J Med* 336: 952-953 [Full Text]
- Wheeler, A. P., Bernard, G. R. (1999). Treating Patients with Severe Sepsis. *N Engl J Med* 340: 207-214 [Full Text]
- Khan, A. A., Slifer, T. R., Araujo, F. G., Suzuki, Y., Remington, J. S. (2000). Protection against Lipopolysaccharide-Induced Death by Fluoroquinolones. *Antimicrob. Agents Chemother.* 44: 3169-3173 [Abstract] [Full Text]
- Weighardt, H., Feterowski, C., Veit, M., Rump, M., Wagner, H., Holzmann, B. (2000). Increased Resistance Against Acute Polymicrobial Sepsis in Mice Challenged with Immunostimulatory CpG Oligodeoxynucleotides Is Related to an Enhanced Innate Effector Cell Response. *J Immunol* 165: 4537-4543 [Abstract] [Full Text]
- Suputtamongkol, Y., Intaranongpai, S., Smith, M. D., Angus, B., Chaowagul, W., Permpikul, C., Simpson, J. A., Leelarasamee, A., Curtis, L., White, N. J. (2000). A Double-Blind Placebo-Controlled Study of an Infusion of Lexipafant (Platelet-Activating Factor Receptor Antagonist) in Patients with Severe Sepsis. *Antimicrob. Agents Chemother.* 44: 693-696 [Abstract] [Full Text]
- Heine, H., Delude, R. L., Monks, B. G., Espevik, T., Golenbock, D. T. (1999). Bacterial Lipopolysaccharide Induces Expression of the Stress Response Genes *hop* and *H411*. *J. Biol. Chem.* 274: 21049-21055 [Abstract] [Full Text]
- Kobold, A. C M., Kallenberg, C. G M, Tervaert, J. W. C. (1999). Monocyte activation in patients with Wegener's granulomatosis. *Ann Rheum Dis* 58: 237-245 [Abstract] [Full Text]
- Zhang, W.-J., Wojta, J., Binder, B. R. (1997). Notoginsenoside R1 Counteracts Endotoxin-Induced Activation of Endothelial Cells In Vitro and Endotoxin-Induced Lethality in Mice In Vivo. *Arterioscler Thromb Vasc Biol* 17: 465-474 [Abstract] [Full Text]
- Kobayashi, S., Kawata, T., Kimura, A., Miyamoto, K., Katayama, K., Yamatsu, I., Rossignol, D. P., Christ, W. J., Kishi, Y. (1998). Suppression of Murine Endotoxin Response by E5531, a Novel Synthetic Lipid A Antagonist. *Antimicrob. Agents Chemother.* 42: 2824-2829 [Abstract] [Full Text]
- Zaks-Zilberman, M., Salkowski, C. A., Elsasser, T., Cuttitta, F., Vogel, S. N. (1998). Induction of Adrenomedullin mRNA and Protein by Lipopolysaccharide and Paclitaxel (Taxol) in Murine Macrophages. *Infect. Immun.* 66: 4669-4675 [Abstract] [Full Text]
- Gleason, T. G., Houlgrave, C. W., May, A. K., Crabtree, T. D., Sawyer, R. G., Denham, W., Norman, J. G., Pruett, T. L. (1998). Hemolytically Active (Acylated) Alpha-Hemolysin Elicits Interleukin-1beta (IL-1beta) but Augments the Lethality of *Escherichia coli* by an IL-1- and Tumor Necrosis Factor-Independent Mechanism. *Infect. Immun.* 66: 4215-4221 [Abstract] [Full Text]
- Zantl, N., Uebe, A., Neumann, B., Wagner, H., Siewert, J.-R., Holzmann, B., Heidecke, C.-D., Pfeffer, K. (1998). Essential Role of Gamma Interferon in Survival of Colon Ascendens Stent Peritonitis, a Novel Murine Model of Abdominal Sepsis. *Infect. Immun.* 66: 2300-2309 [Abstract] [Full Text]
- ARTIGAS, A., BERNARD, G. R., CARLET, J., DREYFUSS, D., GATTINONI, L., HUDSON, L., LAMY, M., MARINI, J. J., MATTHAY, M. A., PINSKY, M. R., SPRAGG, R., SUTER, P. M., the Consensus Committee, (1998). The American-European Consensus Conference on ARDS, Part 2 . Ventilatory, Pharmacologic, Supportive Therapy, Study Design Strategies, and Issues Related to Recovery and Remodeling. *Am J Respir Crit Care Med* 157: 1332-1347 [Abstract] [Full Text]
- Lee, W. J., Farmer, J. L., Hilty, M., Kim, Y. B. (1998). The Protective Effects of Lactoferrin Feeding against Endotoxin Lethal Shock in Germfree Piglets. *Infect. Immun.* 66: 1421-1426 [Abstract] [Full Text]
- Helmerhorst, E. J., Maaskant, J. J., Appelmelk, B. J. (1998). Anti-Lipid A Monoclonal Antibody Centoxin (HA-1A) Binds to a Wide Variety of Hydrophobic Ligands. *Infect. Immun.* 66: 870-873 [Abstract] [Full Text]
- CHESNUTT, A. N., MATTHAY, M. A., TIBAYAN, F. A., CLARK, J. G. (1997). Early Detection of Type III Procollagen Peptide in Acute Lung Injury . Pathogenetic and Prognostic Significance. *Am J Respir Crit Care Med* 156: 840-845 [Abstract] [Full Text]
- Leturcq, D. J., Moriarty, A. M., Talbott, G., Winn, R. K., Martin, T. R., Ulevitch, R. J. (1996). Antibodies against CD14 Protect Primates from Endotoxin-induced Shock. *J. Clin. Invest.* 98: 1533-1538 [Abstract] [Full Text]
- Taylor, A. H., Heavner, G., Nedelman, M., Sherris, D., Brunt, E., Knight, D., Ghrayeb, J. (1995).

Lipopolysaccharide (LPS) Neutralizing Peptides Reveal a Lipid A Binding Site of LPS Binding Protein. *J. Biol. Chem.* 270: 17934-17938 [\[Abstract\]](#) [\[Full Text\]](#)

- Kiani, A., Tschiersch, A., Gaboriau, E., Otto, F., Seiz, A., Knopf, H.-P., Stütz, P., Färber, L., Haus, U., Galanos, C., Mertelsmann, R., Engelhardt, R. (1997). Downregulation of the Proinflammatory Cytokine Response to Endotoxin by Pretreatment With the Nontoxic Lipid A Analog SDZ MRL 953 in Cancer Patients. *Blood* 90: 1673-1683 [\[Abstract\]](#) [\[Full Text\]](#)

[HOME](#) | [SEARCH](#) | [CURRENT ISSUE](#) | [PAST ISSUES](#) | [COLLECTIONS](#) | [HELP](#)

Comments and questions? Please [contact us](#).

The New England Journal of Medicine is owned, published, and [copyrighted](#) © 2005 [Massachusetts Medical Society](#). All rights reserved.